# Accelerated progression of carotid stenosis in patients with previous external neck irradiation

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***Objective:*** **Radiotherapy to the head and neck often results in carotid stenosis, but the course of disease is unknown. We investigated the natural history and progression of asymptomatic carotid stenosis induced by external irradiation.**
***Patients and Methods:*** **The study included 130 carotid arteries in 95 patients who had received external radiation therapy to the head and neck area and who had asymptomatic, mild internal carotid artery or common carotid artery stenosis. Stenosis of 15% to 49% on duplex ultrasound (US) scans defined mild (<50%) disease. Another 95 arteries in 74 patients with matched degree of carotid artery stenosis but who had not received radiation therapy were used as control. Both groups were followed up prospectively with serial duplex US scanning, and degree of carotid artery stenosis was categorized as 15% to 49%, 50% to 69%, 70% to 99%, and occlusion. Progression of carotid artery stenosis was defined as increase in stenosis from less than 50% to 50% or greater at ultrasonography. Secondary end points included progression to higher disease category, new cerebrovascular symptoms, and death. Data from irradiated arteries was compared with control data with the life table method. A Cox regression model was used to analyze disease progression, adjusted for covariates of sex, age, smoking, diabetes, and hypertension.**
***Results:*** **Mean follow-up was 36 months. Adjusted freedom from progression rates at 3 years were 65% for irradiated arteries and 87% for control arteries at life-table analysis ($P = .035$; odds ratio, 3.1). The annualized progression rate from less than 50% to 50% or greater in irradiated arteries was 15.4%, compared with 4.8% in nonirradiated arteries. A long history of cervical irradiation (>6 years) was the only significant risk factor for disease progression. There was no difference between the two groups regarding development of new symptoms or mortality.**
***Conclusions:*** **Carotid stenosis associated with external irradiation progresses more rapidly compared with nonirradiated atherosclerotic arteries. Aggressive surveillance is recommended. (J Vasc Surg 2004;39:409-15.)**

External cervical radiation therapy for head and neck cancer is associated with injury to the extracranial carotid arteries through direct intimal damage, periadventitial fibrosis, and obliteration of the vasa vasorum. These features lead to premature atherosclerosis that involves more extensive areas of the common and internal carotid arteries, corresponding to the field of irradiation. Several cross-sectional studies with duplex ultrasound (US) scanning have demonstrated that significant carotid stenosis occurs in 12% to 22% of patients who have undergone neck irradiation.[1,2] However, the outcome and rate of disease progression is not well known, and is assumed to be similar to that of general atherosclerosis.

Whereas severe or symptomatic stenosis in previously irradiated carotid arteries may be managed with the same principles as nonirradiated arteries, management of asymptomatic mild to moderate carotid artery stenosis has not been addressed. Retrospective studies indicate that radiation-associated carotid disease may not follow a benign course, and cerebrovascular symptoms are more prevalent.[1,3] No clear guidelines exist as to whether patients who have received external cervical radiation therapy, yet with clinically insignificant disease, should be monitored with serial duplex US scanning or given more aggressive therapy. With continuing improvement in treatment and survival of patients with head and neck cancer, radiation-induced carotid artery stenosis has become an important aspect of vascular surgery practice. A prospective natural history study of carotid artery disease associated with previous neck radiation therapy will provide some answer to these issues.

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## PATIENTS AND METHODS

From October 1997 to January 2002, a carotid US follow- up study was conducted in the Department of Surgery in patients who had received external radiotherapy to the head and neck because of malignancy. Subjects were recruited from a duplex US scanning screening program in patients from the follow-up registry of the Division of Head and Neck Surgery and Otorhinolaryngology. Patients who met criteria for inclusion had received external radiation therapy to the ipsilateral neck, were without previous cerebrovascular symptoms, and had initial carotid artery stenosis less than 50% at enrollment. Carotid artery disease less than 50% is defined in this study as stenosis of 15% to 49% at duplex US scanning. Patients were excluded if they had no carotid artery stenosis or the initial stenosis exceeded 50%, had undergone carotid surgery or other forms of intervention, or declined to participate in the study. Most patients (>80%) had nasopharyngeal, oropharyngeal, or laryngeal cancers, and had undergone a standard protocol

of external radiotherapy with bilateral cervical irradiation with 60 Gy to the primary lesion and 50 to 60 Gy to both sides of the neck, depending on regional lymph node status.

Initial duplex US scanning was performed in 221 patients who had received neck radiotherapy but did not have previous symptoms of cerebrovascular disease. Of the 442 asymptomatic arteries examined, 312 were excluded from the present trial because there was insignificant (<15%) or no disease (n = 236) or because stenosis exceeded 50% (50%-69%, n = 33; range, 70%-99%, n = 35, carotid occlusion, n = 8). The remaining 95 patients, with asymptomatic, mild (15%-49%) carotid stenosis, were recruited into the prospective serial color-flow Doppler US screening follow- up program. All patients were followed up for at least 6 months and underwent at least two consecutive duplex US scanning examinations.

A control group of asymptomatic patients with mild (<50%) carotid artery stenosis but who had not received radiotherapy or undergone carotid artery surgery was made up of consecutive patients with known atherosclerotic carotid artery disease detected incidentally at screening, and were followed up in our vascular laboratory during the same period. Carotid artery stenosis in the control subjects paralleled that of the radiotherapy group, but they were not matched for gender or age.

Demographic data and standard risk factors for atherosclerosis (smoking, diabetes, hypertension, cardiovascular comorbidity) were obtained at recruitment. All patients and control subjects received maintenance anti-platelet therapy in the form of aspirin (100 mg/d).

**Color flow Doppler US scanning.** All patients and control subjects underwent color flow Doppler US scanning (Acuson 128XP-10 system, 5 MHz probe; Acuson, Mountain View, Calif) by a single registered vascular technologist in our vascular laboratory. Percent stenosis of the common and internal carotid arteries was determined with standard criteria based on peak systolic and end-diastolic velocity, and internal carotid artery/common carotid artery ratio.[4] For this analysis the degree of carotid stenosis was classified into four categories: 15% to 49%, 50% to 69%, 70% to 99%, and occlusion. In patients with both internal and common carotid artery disease, the higher degree of arterial stenosis was chosen. Sensitivity and specificity of the laboratory were previously validated with conventional carotid angiography to be 93% and 86%, respectively, for detection of greater than 70% stenosis. Subjects were followed up with duplex US scanning every 6 months, and, if new symptoms developed, more frequently, as indicated. During each visit a history regarding development of new symptoms was obtained and a clinical examination was performed. New cerebrovascular events were documented at computed tomography (CT), magnetic resonance imaging (MRI), or both, and were recorded as new events only if there were definite symptoms referable to the middle cerebral artery territory or if new ischemic changes were demonstrated on cerebral images.

**Disease progression and statistical analysis.** Disease progression was defined as an increase in degree of carotid artery stenosis from less than 50% to 50% or greater, with two additional end points of progression to 70% or greater, and occlusion. Carotid artery duplex US scanning data were analyzed with the life table method, with disease progression as the terminal event. Results were expressed by cumulative freedom of disease progression, and displayed as an actuarial life table, both from enrollment and extrapolated to the time of initial radiotherapy. Survival curves were plotted to the point where standard error of cumulative freedom of progression exceeded 10%. Additional secondary end points were new cerebrovascular symptoms and death. Disease progression rate between groups was compared with the generalized Wilcoxon (Gehan) test. $P = .05$ was considered statistically significant.

To identify significant risk factors for disease progression, a separate analysis was performed within the radiotherapy group and the control group, with the life table method. Variables examined included age (60 years or older), gender, smoking, diabetes, hypertension, cardiac comorbidity in both groups, and previous neck surgery, common carotid artery involvement, and interval from initial radiotherapy in the radiotherapy group. Disease progression was compared between the radiotherapy group and the control group, with a Cox regression model adjusted for potential confounding factors as listed, and adjusted hazards ratio (relative risks) was determined for significant factors.

All statistical analysis, and actuarial and Cox proportional hazards plots were performed with SPSS version 9.0 (SPSS, Chicago, Ill).

**Table I.** Site of primary malignancy in 95 patients with cervical irradiation

| *Site of primary malignancy* | *n* | *%* |
|---|---|---|
| Nasopharynx | 44 | 46.3 |
| Larynx | 23 | 24.2 |
| Oral cavity | 8 | 8.4 |
| Tongue | 4 | 4.2 |
| Parotid | 4 | 4.2 |
| Hypopharynx | 3 | 3.2 |
| Paranasal sinuses | 2 | 2.1 |
| Miscellaneous | 7 | 7.3 |
| Total | 95 | 100.0 |

## RESULTS

Ninety-five patients (130 arteries) with irradiation-induced carotid artery stenosis were included in the study. Seventy patients were men, and 25 patients were women; mean age was 60 ± 15 years (range, 19-86 years). Sites of primary head and neck lesions are listed in Table I, and clinical characteristics are shown in Table II. Patients had received a standard radiotherapy regimen of 60 Gy to the primary lesion and 60 Gy to the ipsilateral neck, on average for 7.6 years (±6.4 years) before presentation. Sixty-six patients (69%) had undergone previous surgery to the head and neck: resection of the primary tumor in 46 patients, and total laryngectomy in 20 patients. Thirty patients under-

**Table II.** Clinical characteristics of patients with radiation-induced carotid artery stenosis and controls subjects

| | *Radiotherapy group (n = 95)* | | *Control group (n = 74)* | | |
|---|---|---|---|---|---|
| | *n* | *%* | *n* | *%* | P |
| Coronary artery disease | 2 | 2 | 20 | 21 | <.01 |
| Diabetes mellitus | 7 | 5 | 34 | 36 | <.01 |
| Hypertension | 23 | 18 | 56 | 59 | <.01 |
| Smoking | 41 | 32 | 48 | 51 | .12 |

went radical neck dissection ipsilateral to the carotid artery studied.

The control group comprised 43 men and 31 women, with mean age of 69 ± 9 years (range, 39-88 years). All study subjects had mild (<50%) stenosis in one or both internal carotid arteries on initial duplex US scans. Because atherosclerotic carotid artery stenosis is less common in younger persons, we were not able to recruit a control group age-matched to the radiotherapy group. Control subjects were therefore slightly older, with a smaller proportion of men and a higher incidence of atherosclerosis-related risk factors and comorbid conditions, compared with patients with radiation-induced carotid artery stenosis (Table II).

**Progression of carotid artery stenosis.** Mean follow-up was 36 months (range, 6-68 months) in the radiotherapy group and 30 months (range, 6-73 months) in the control group. On average, 4.3 duplex US scans were obtained per carotid artery. Progression of carotid artery stenosis from less than 50% to 50% or greater occurred in 43 irradiated arteries (33%) and 22 control arteries (23%) during follow-up (Table III). Stenosis progressed to 70% or greater in only nine arteries (7%) in the radiotherapy group and six arteries (6%) in the control group. Only two patients in the radiotherapy group and one patient in the control group had duplex US scan evidence of progression to occlusion. In the radiotherapy group disease progressed (>50%) in 19 internal carotid arteries (44%) and 17 common carotid arteries (40%), and in both the internal and common carotid arteries in 7 patients (16%).

Life table survival curves of cumulative freedom from disease progression from less than 50% to 50% or greater in the radiotherapy and control groups are shown in Fig 1. Comparison of the two groups with the generalized Wilcoxon test showed that progression of carotid artery stenosis in irradiated arteries was significantly faster than in control arteries ($P = .035$).

Cox regression plots for disease progression, adjusted for potential confounding covariates, are shown in Fig 2. Adjusted freedom from progression rate at 3 years was 65% for irradiated arteries and 87% for control arteries (odds ratio, 3.1). The adjusted annualized progression rate for carotid artery stenosis less than 50% to 50% or greater was 15.4% in patients who had undergone head and neck radiation therapy, compared with 4.8% in control subjects.

**Table III.** Natural history of mild (<50%) carotid artery stenosis in irradiated and control arteries

| | *Radiotherapy group (n = 130)* | | *Control group (n = 95)* | |
|---|---|---|---|---|
| | *n* | *%* | *n* | *%* |
| Progression to >50% | 43 | 33 | 22 | 23 |
| Progression to >70% | 9 | 7 | 6 | 6 |
| Progression to occlusion | 2 | 2 | 1 | 1 |
| New symptoms | 4 | 3 | 8 | 8 |

**Relationship between carotid artery disease progression and time since radiotherapy.** Univariate analysis with the life table method confirmed that age, gender, smoking, diabetes, hypertension, and cardiovascular comorbidity individually were not associated with significant differences in disease progression within either the radiotherapy group or the control group. Disease progression was also independent of common carotid artery involvement and previous neck surgery in irradiated arteries.

There was a positive relationship of disease progression with the interval between radiotherapy and the first carotid US examination. Progression from less than 50% to 50% or greater occurred significantly faster in patients who had undergone neck irradiation more than 6 years previously (group median) compared with those with a shorter history of previous radiotherapy ($P = .02$; Fig 3).

**New symptoms and interventions.** In 11 patients, three in the radiotherapy group and eight in the control group, new cerebrovascular symptoms developed, localized to the ipsilateral hemisphere and confirmed at CT or MRI. There was no relation between new symptom development and degree of carotid stenosis or presence of disease progression. Only one carotid artery in the radiotherapy group and four of eight carotid arteries in the control group exhibited evidence of disease progression greater than 50% at the time of new symptom development. Our policy is to recommend cerebral revascularization in patients if stenosis reaches 70% in symptomatic disease and 80% in asymptomatic disease. Carotid endarterectomy is the standard treatment in our institution, except in patients who have undergone neck radiotherapy, for whom carotid angioplasty and stenting is the preferred option. Among the relatively small number of patients with significant or symptomatic disease, no patients in either group consented to revascularization of the corresponding artery.

Four patients in the control group died of stroke (n = 2) or cardiac disease (n = 2). Seven patients in the radiotherapy group died during the study, six with malignancy and one with cardiac failure.

## DISCUSSION

Cross-sectional and retrospective studies have shown that patients with previous radiotherapy to the neck area are

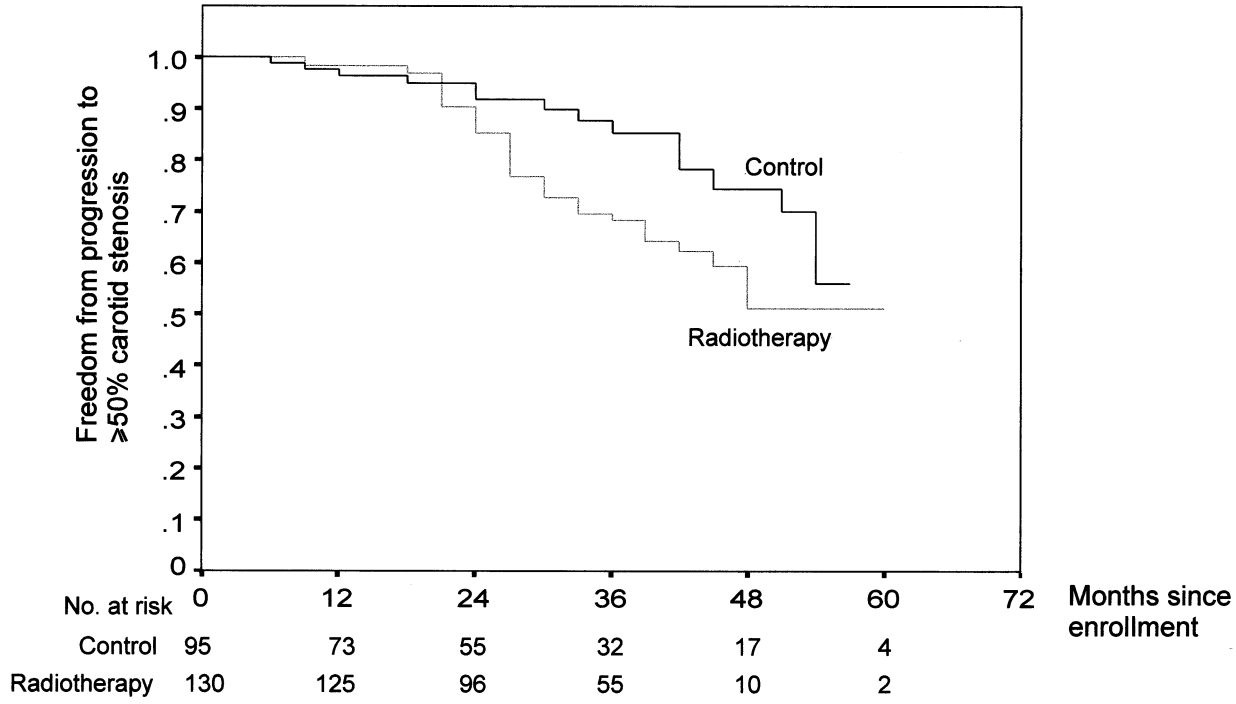


**Fig 1.** Life table plots of freedom from disease progression from mild (<50%) carotid stenosis to 50% or greater stenosis in radiotherapy and control groups ($P = .035$).

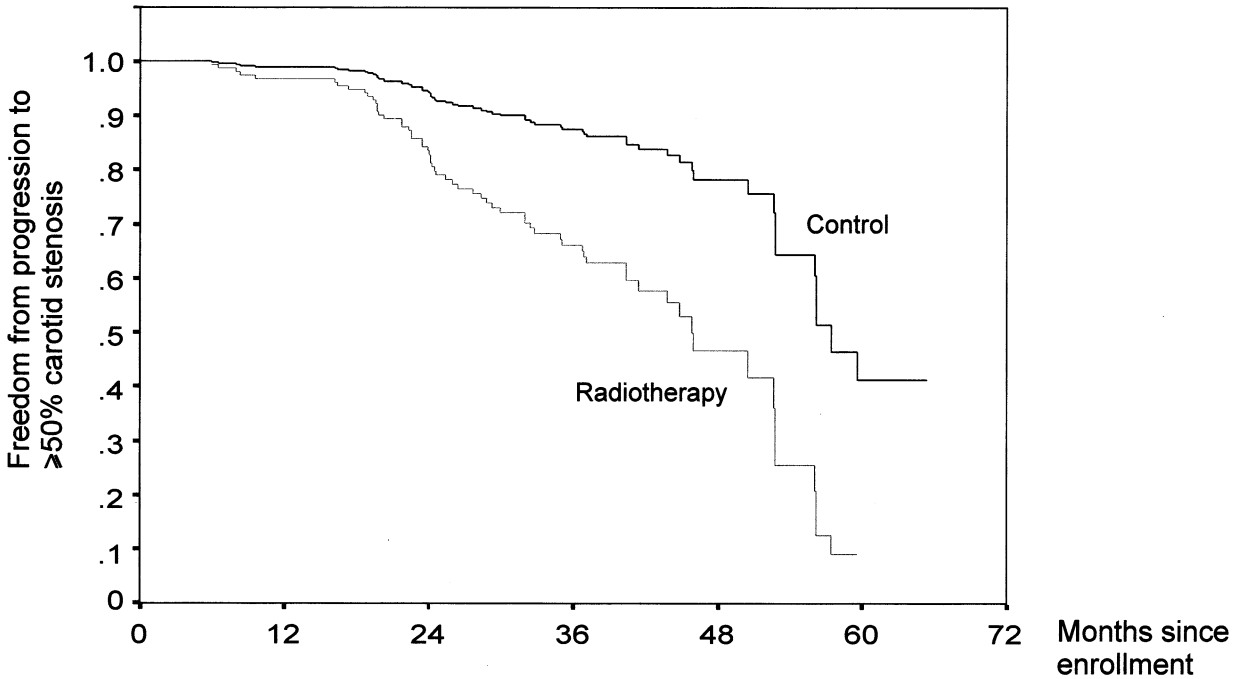


**Fig 2.** Cox regression curves of freedom from progression from mild (<50%) carotid stenosis to 50% or greater stenosis in radiotherapy and control groups, adjusted for confounding risk factors.

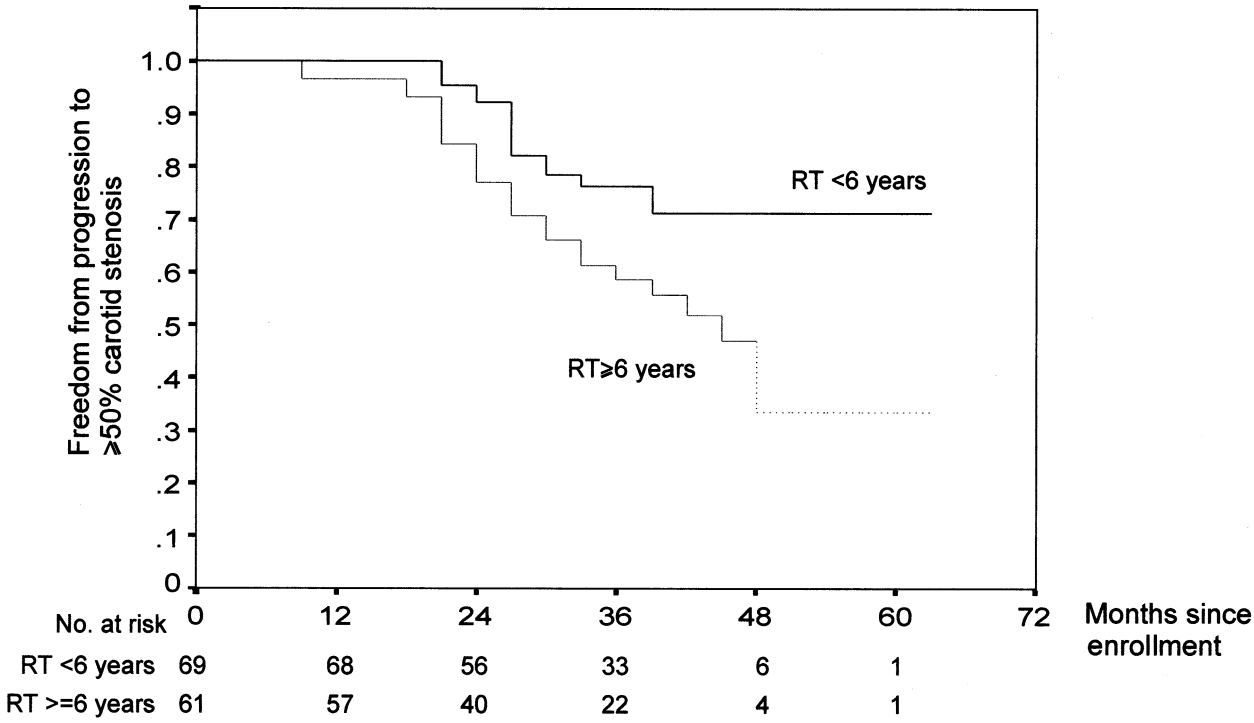


**Fig 3.** Disease progression in irradiated carotid arteries, stratified by interval from initial radiotherapy.

at risk for significant carotid artery stenosis, with symptoms in a high proportion (17%).[1,2] A direct causal effect of radiation injury and subsequent development of carotid stenosis, however, has not been established, because clinically detectable carotid artery stenosis occurs only several years after radiotherapy. Doubt remains as to whether radiation-induced carotid artery disease is merely an early manifestation of atherosclerosis or is an association rather than a sequela. In the past, many patients who had received cervical radiation therapy died of the malignancy before cerebrovascular complications were manifested, and the added risks of carotid endarterectomy in this group of patients do not justify routine screening. Although carotid endarterectomy in patients with previous neck radiation therapy may not be associated with higher risk for stroke,[5,6] the procedure is inherently more difficult, because of fibrosis and arteritis, resulting in more cranial nerve palsy[5] and artery damage necessitating graft replacement.[6] New treatment methods such as carotid angioplasty and stenting have shown promise as preferred minimally invasive alternatives, and can be performed safely and provide at least short-term benefit in these patients.[7] Critical appraisal of the disease is therefore necessary.

In this prospective longitudinal observational study, we found that carotid artery stenosis progresses more rapidly in irradiated carotid arteries compared with control arteries with similar degree of initial disease, at a relative risk of 3.1 and an annual rate of 15.4%. To better study the influence of radiation free from extraneous influences, such as critical hemodynamics and irregular plaque, we included only subjects with asymptomatic mild stenosis. Our results suggest that radiation-induced carotid artery stenosis is not attributable to premature atherosclerosis alone, but is a more aggressive disease with a different biologic behavior. The injurious effect of external irradiation is lasting, and is more pronounced after 6 or more years of follow-up after radiotherapy.

Historical data from studies on the course of carotid artery stenosis in patients with general atherosclerosis show a consistent annual progression rate of 3% to 5%. Liapis et al[8] reported that progression of carotid artery stenosis less than 50% in patients with asymptomatic disease was 16% in 3 years. In a study of 1004 patients with asymptomatic disease with serial duplex US scanning, Muluk et al[9] observed an annualized rate of progression from mild (<50%) to greater than 50% stenosis of 3.3%. Another group of investigators showed in a longitudinal follow-up study of up to 10 years that carotid artery stenosis less than 50% progressed slowly, at a rate of 21% over 7 years.[10] Hypertension and low serum high-density lipoprotein levels have been reported as significant determinants of disease progression.[9,11] The Oregon study on progression of disease in patients with asymptomatic internal carotid artery stenosis from less than 60% to 60% to 99% reported a 24-month progression rate of 30% in patients with peak internal carotid artery systolic velocity greater than 175 cm/s, but only 5% in the less than 175 cm/s group.[12] The annual rate of progression of 4.8% in our control population is compa-

rable to these literature reports, and supports the observation that radiation-induced carotid artery stenosis progresses at a faster rate.

A few possible mechanisms may explain the faster progression of disease in irradiated arteries. In a prospective observational study on the immediate effect of radiation on the carotid artery, Muzaffar et al[13] demonstrated that neck irradiation significantly increases the thickness of the carotid artery wall during the first year after radiation therapy, and the changes appear to be progressive. This thickening may lead to considerable luminal reduction. Damage to the vasa vasorum may be irreversible and present a continuous ischemic stimuli to the vessel wall. The field of irradiation damage is more widespread, and often involves the common and internal carotid arteries. As a result of more extensive disease the plaque surface area is increased, leading to more rapid platelet deposition and disease progression. Concomitant common carotid artery stenosis can also limit flow and induce turbulence in the internal carotid artery, and hasten the atherosclerotic process.

Our control group consisted of patients with asymptomatic less than 50% stenosis. Inasmuch as atherosclerosis tends to occur in older persons, in whom comorbidity and risk factors are more prevalent than in patients with radiation-induced stenosis, it is not possible to obtain a control group matched for age and risk factors. A Cox proportional hazards model was used to adjust for the effect of standard confounding variables. We believe this imbalance in age and concomitant risk factors would only bias disease progression in favor of the control subjects.

Evidence from large randomized studies indicates that the risk for stroke in patients with asymptomatic mild carotid artery stenosis is low, and routine follow-up is not cost effective. In the multicenter Asymptomatic Cervical Bruit Study, the annual rate of all primary vascular events was 4.2% in the group with less than 50% stenosis.[14] A clinical follow-up study from the North American Symptomatic Carotid Endarterectomy Trial on contralateral asymptomatic carotid stenosis of less than 60% showed the risk for stroke at 5 years is 8%, only 1.6% annually.[15] Retrospective studies of asymptomatic moderate (60%-79%) carotid artery stenosis from The Cleveland Clinic reported a 3-year progression rate of 20% and an ipsilateral stroke rate of only 2.4%. However, patients with disease progression were more likely to have symptoms.[16] Progression of disease has also been identified as a significant predictor of future stroke in patients with asymptomatic 50% to 79% stenosis.[17] Liapis et al[18] demonstrated that progressive lesions were associated with increased risk for neurologic events in a group of largely (66%) asymptomatic patients with less than 50% stenosis, for an annual risk for stroke of 3%. With its faster rate of progression, it is likely that radiation-induced carotid artery stenosis results in a higher risk for stroke.

One limitation of this study was that patients were enrolled on average 7 years after neck irradiation. It is difficult to instigate a prospective study of carotid arteries immediately after radiotherapy, because carotid artery stenosis develops over time. In addition, there would be a substantial drop-off rate as a result of death from malignancy, and any benefits from such a screening program would be offset by reduced survival.

We were not able to show a difference in the incidence of stroke in this study, because follow-up was not sufficiently long for more severe disease (>70%) to develop. One issue that long-term studies will have to include is that many patients who have received radiation therapy to the head and neck area also have other sequelae of radiation injury, such as temporal lobe necrosis and otitis media. These complications may produce nonspecific neurologic symptoms that render evaluation of cerebral ischemia difficult. In our series only those patients with imaging-proved ischemic disease were regarded as having new symptoms. Such an event was uncommon, and was not associated with degree of carotid artery stenosis. The paradoxical finding of a higher rate of new cerebrovascular symptoms in the control group despite a relative lack of progression to significant carotid artery stenosis can be explained by their being older and having more risk factors and intracranial disease. We can also speculate that radiation-induced carotid plaque may be more fibrotic and contain less lipid, thus having less embolic potential. A study to differentiate radiation-induced carotid plaque from atherosclerotic plaque with ultrasonic characterization, however, showed that they had similar echomorphologic features.[19] The number of patients with disease progressing to significant stenosis was small, and no definitive conclusion can be drawn regarding symptoms. The definitive answers as to whether there would be further disease progression to critical stenosis and whether one should treat more aggressively for stroke prevention remain to be addressed by future long-term observation of this cohort. Meanwhile, we recommend a higher level of alert and routine surveillance with ultrasonography in all patients with carotid artery stenosis induced by radiation therapy.

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